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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,485	10/17/2001	Brenda F. Baker	RTS-0139	5056

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	4

DATE MAILED: 09/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,485	BAKER ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-2 and 11 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Farr et al. (US Patent No. 5,811,231).

Claim 1 recites a compound of 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding matrix metalloproteinase 1 (SEQ ID NO: 3), wherein said compound specifically hybridizes with said nucleic acid molecule encoding matrix metalloproteinases 1 and inhibits the expression of matrix metalloproteinases 1. Claim 2 recites the compound of claim 1 which is an antisense oligonucleotide. Claim 11 recites a compound 8 to 50 nucleobases in length which specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding matrix metalloproteinases 1.

Farr et al. discloses an oligonucleotide primer of 20 nucleotides in length, that is the reverse complement (i.e. antisense) to nucleotides 49 to 68 of the nucleic acid encoding matrix metalloproteinases 1 (MMP-1) mRNA according to SEQ ID NO: 3 of the instant application (See col. 28, line 47, SEQ ID NO: 45 of Farr et al.). Since the oligonucleotide primer of Farrr et al. meets all the structural requirements of the instant claims, the oligonucleotide primer according to SEQ ID NO: 45 of Farr et al. would also be expected to specifically hybridize to

nucleic acid encoding matrix metalloproteinases 1, as per applicant's definition of "specifically hybridize" set forth in the specification as filed, page 8, line 37, through page 9, lines 1-11.

Since the prior art oligonucleotides meet all the structural limitations of the claims, the prior art oligonucleotides would then be considered to "inhibit expression" of the gene as claimed, absent evidence to the contrary. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims."

Therefore, the instant invention is anticipated or obvious over Farr et al.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-2, and 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khaw et al. in view of Brinckerhoff et al. and Monia et al.

The instant claims read on a compound of 8 to 50 nucleobases in length that specifically hybridizes to a nucleic acid molecule encoding matrix metalloproteinase 1 (SEQ ID NO: 3), wherein the compound is an antisense oligonucleotide, comprises a modified internucleoside linkage, such as a phosphorothioate linkage, a modified nucleobase, such as a 5-methylcytosine, or a modified sugar moiety such as a 2'-O-methoxyethyl sugar moiety, or further wherein the antisense oligonucleotide is a chimeric oligonucleotide. Additionally, the instant claims read on a composition comprising the compound of 8 to 50 nucleobases in length and a pharmaceutically acceptable carrier or diluent, wherein the compound is an antisense oligonucleotide, or further wherein the composition is a colloidal dispersion system.

Khaw et al. describe matrix metalloproteinases (MMP) inhibitors, especially collagenase inhibitors, and their use in the manufacture of a medicament for the treatment of a natural or artificial tissue comprising extracellular matrix components to inhibit contraction of the tissue and methods for the treatment of tissue comprising extracellular matrix components to inhibit contraction (see col. 1, lines 13-16). The MMP inhibitors are designed to inhibit MMP's including MMP-1 (also called collagenase), see col. 1, lines 41-50.

According to Khaw et al. an antisense molecule need not be large; 20 base pairs is often sufficient. If the molecule is small it should be able to enter the cells unaided but liposomes can be used to assist entry if required. An antisense molecule will usually be designed to attach to the MMP mRNA but may be designed to attach to the appropriate DNA during replication and transcription (col. 9, lines 28-38). Gels and liposomes may be the preferred delivery method when the inhibitor is an antisense molecule (col. 10, lines 56-57).

However, Khaw et al. does not disclose compounds targeted to the nucleotide sequence of SEQ ID NO: 3, or the antisense oligonucleotide compounds according to the present invention comprising at least one modified internucleoside linkage, wherein said linkage is a phosphorothioate linkage, or comprising a 2'-O-methoxyethyl modified sugar, a 5-methylcytosine modified nucleobase, a chimeric oligonucleotide, or a composition comprising said antisense oligonucleotide compounds further comprising a colloidal dispersion system.

The nucleotide sequence of matrix metalloproteinase 1 (MMP-1), which is SEQ ID NO: 3 of the instant application, was determined by Brinckerhoff et al. (See Figure 1A-B; Brinckerhoff et al., J. Clin. Invest., 1987, 79, 542-546).

Monia et al. teach the design of antisense oligonucleotides comprising various modifications, including phosphorothioate modified internucleoside linkages (col. 8, line 41-43), 2'-O-methoxyethyl sugar modifications (col. 10, line5), 5-methylcytosine modified nucleobase (col. 10, line 31-32), and wherein the antisense oligonucleotide is a chimeric oligonucleotide (col. 11, line 51). The modified or substituted oligonucleotides of Monia et al. are preferred over native (unmodified or unsubstituted) forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced binding to target and increased stability in the presence of nucleases (col. 8, lines 2-6). Additionally, Monia et al. teach the use compositions comprising antisense oligonucleotides and a pharmaceutically acceptable carrier or diluent, and further comprising a colloidal dispersion system in order to enhance the stability of oligonucleotides introduced into cells and to target oligonucleotides to a particular tissue or cell (col. 15, lines 19-41).

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the teachings of Khaw et al. with the teachings of Brinckerhoff et al. and Monia et al. to design the compounds and compositions according to the present invention. One of ordinary skill in the art would have been motivated to design antisense compounds targeted to the nucleotide sequence of SEQ ID NO: 3, which encodes MMP-1, because Khaw et al. expressly states motivation to design antisense oligonucleotides targeting MMP-1 (col. 9, lines 28-38), and Brinckerhoff et al. provides the nucleotide sequence. Moreover, one of ordinary skill in the art would have been motivated to modify the antisense oligonucleotides of Khaw et al. to comprise phosphorothioate modified internucleoside linkages, 2'-O-methoxyethyl sugar modifications, 5-methylcytosine modified nucleobases, or wherein said antisense compound is a chimeric compound, because, according to Monia et al., antisense oligonucleotides comprising these modifications would enhance the cellular properties of antisense oligonucleotides as compared to unmodified antisense compounds. Moreover, one of ordinary skill in the art would have been motivated to design compositions comprising the antisense compounds according to the present invention and a pharmaceutically acceptable carrier or diluent, and further comprising a colloidal dispersion system because Monia et al. teach that compositions designed according to this manner would enhance the stability of oligonucleotides introduced into cells and would help to target oligonucleotides to a particular tissue or cell.

Therefore, the invention as a whole is *prima facie* obvious over Khaw et al. in view of Brinckerhoff et al. and Monia et al.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

7. The instant claim recites a compound 8 to 50 nucleobases in length which specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding matrix metalloproteinase 1.

According to the specification as filed, page 9, lines 1-11, an antisense compound is "specifically hybridizable when binding of the compound to the target DNA or RNA molecule interferes with the normal function of the target DNA or RNA to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target sequences under conditions which specific binding is desired, i.e., under physiological conditions in the case of *in vivo* assays...." Moreover, the specification as filed states that "[I]t is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable." (page 8, line 37, through page 9, line 1).

The instant claims encompass compounds of 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding matrix metalloproteinase 1, including all forms of matrix

metalloproteinase 1 nucleic acid isolated from all sources, including all polymorphic, allelic and splice variants of this nucleic acid. Moreover, in order for the claimed compound to "specifically hybridize" to all forms of nucleic acid encoding matrix metalloproteinase 1, wherein said compound is of sufficient complementarity to all forms of matrix metalloproteinase 1, avoid non-specific binding to other sequences, and interfere with the normal function of the target nucleic acid sequence, the skilled artisan would have to know the structure of all forms of nucleic acid encoding matrix metalloproteinase 1 in order to design the compounds of the present invention. Applicants provide only a description of compounds according to the present invention which target nucleic acid encoding human matrix metalloproteinase 1 according to SEQ ID NO: 3.

The compounds according to the present invention which target SEQ ID NO: 3 can not be used to predict the structures of compounds which would be effective to "specifically hybridize" to forms of matrix metalloproteinase 1 isolated from other organisms since functional antisense compounds can only be identified empirically. Moreover, in regards to the term "active site" recited in the instant claim, page 9, of the specification as filed, lines 12-21, states "[A]ntisense and other compounds of the invention which hybridize to the target and inhibit expression of the target are identified through experimentation, and the sequences of these compounds are hereinbelow identified as preferred embodiments of the invention. The target sites to which these preferred sequences are complementary are hereinbelow referred to as "active sites" and are therefore preferred sites for targeting. Therefore another embodiment of the invention encompasses compounds which hybridize to these active sites." Based upon this passage of the specification as filed, it is clear that further experimentation would be required in

order to identify compounds 8 to 50 nucleobases in length which specifically hybridize to an active site on other forms of nucleic acid encoding a matrix metalloproteinase 1, not encompassed by SEQ ID NO: 3 according to the present specification.

See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Additionally, MPEP § 2163 [R-1] states "The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for

written description purposes, even when accompanied by a method of obtaining the claimed sequence."

Applicant's specification does not provide a sufficient description of all embodiments encompassed by the claimed compounds, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds. Moreover, it is apparent that further experimentation is required to identify the structures of all embodiments encompassed by the instant claims. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of the full scope of compounds encompassed by the instant claims at the time of filing of this application.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Fri, 8:30AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
September 4, 2003